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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
O'HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,192	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 3, 2006 has been entered.

Claims Status

2. Claims 58-62 are pending in the instant application.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 and 112, first paragraphs read as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 58-62 remain rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed May 20, 2004, December 15, 2004, November 14, 2005 and below.

Claims 58-62 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants' arguments (pages 4-15, Paper filed August 3, 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicants rely on the gene amplification data for the gene encoding PRO274 polypeptide for patentable utility of the PRO274 polypeptide and the claimed antibodies that bind it. The issue is whether or not amplified DNA correlates with increased mRNA, and whether or not increased mRNA levels correlates with increased protein levels. The art establishes that there is no strong correlation between gene amplification and increased mRNA or protein levels. See Pennica et al., and Gygi et al. of record.

Applicants submit that they have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level, and that the articles by Ornfoft et al., Hyman et al., and Pollack et al. (of record) collectively teach that in general, gene amplification increases mRNA expression. Applicants also submit that the Declaration of Dr. Paul Polakis shows that in general there is a correlation between mRNA levels and polypeptide levels. In the Declaration Dr. Polakis states that antibodies binding to about 30 tumor antigens that were more highly expressed in tumor cells compared to corresponding normal cells as determined by microarray were prepared, and in approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA. Applicants

submit Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

Applicants present a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data, which identifies 28 gene transcripts out of 31 gene transcripts that showed good correlation between tumor mRNA and tumor protein levels, and argue that case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.

The second declaration of Dr. Polakis under 37 CFR 1.132 filed on August 3, 2006 is acknowledged, and it is insufficient to overcome the following rejection of claims 58-62 based upon lack of utility under 35 U.S.C. 101, and lack of enablement under 35 U.S.C. 112, first paragraph.

The second Polakis Declaration indicates that 31 antibodies have been used to quantitatively determine the level of tumor antigen proteins in both human tumor tissue and normal tissue, and the levels of mRNA and protein in both the tumor and normal tissues have been quantitatively compared and that Exhibit B shows that the 31 genes over expressed in human tumor tissue at the mRNA level, and 28 of them are also detectably over expressed in human tumor tissue at the protein level, thus, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded thereby. The declaration further indicates that, based on personal scientific opinion, an increased level of mRNA in a

tumor tissue relative to a normal tissue more often than not correlates to a similar increase in abundance of the encoded protein (item 6). This has been fully considered but is not found to be persuasive because PRO274 does not appear in the table of Exhibit B, and thus, it is unclear how the result in Exhibit B is related to the present PRO274. Further, the declaration provides no information as to what those tumor antigens that do correlate (mRNA and proteins levels) have in common, and in the absence of such, one may not extrapolate that the PRO274 would share the same characteristics as those tested. Furthermore, even if the result is relevant, there is no numerical data on what significant over expression is, but "+" or "-", wherein "+" merely means "detectably" over expressed as explained in the declaration. As such, the examiner could not independently evaluate the results. For example, how many tumor samples were analyzed, among which how many are lung tumors (as is PRO274), what are the levels of expression of the PRO274 mRNA/protein in cancer vs. non-cancerous tissues, what the "detectably" over expressed level really means, and whether it is statistically meaningful? For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? The declaration states that levels of mRNA and protein in tumor tissue were compared to corresponding normal tissue, but the amplification levels of genomic DNA from example 114 were compared to normal human blood, not corresponding normal tissue.

Furthermore, the fact that some samples showed no correlation is consistent with what the prior art has established, i.e., it is not predictable whether an increase of mRNA expression of a specific gene is correlated to the increase of the protein levels.

Therefore, in the absence of any evidence directly associated with the claimed PRO274, and a knowledge of what those that do correlate have in common, the declaration is insufficient to overcome the rejections of the claims under 35 U.S.C. 101, and 35 U.S.C. 112, first paragraph.

With respect to Dr. Polakis's personal scientific opinion, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not the increased mRNA levels is predictive of increased protein levels. (2) The instant specification only discloses the measurement of PRO274 mRNA, and does not disclose any information regarding PRO274 protein levels. There is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., the Chen reference (cited in the previous Office Action), which reports only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, factual support for the expert's opinion is absent as data disclosed in the declaration is not related to the presently claimed PRO274, the statistical significance of the result from other tumor genes is unclear, and no numerical data are included in the declaration so that the examiner could not independently evaluate them. As such, the declaration of Dr. Polakis

under 37 CFR 1.132 is insufficient to overcome the rejections of the claims under 35 U.S.C. 101, and 112, first paragraph.

Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc., pages 7-14). Applicant asserts that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants submit a total of 118 references in addition to the declarations and references already of record which they assert supports Applicants' asserted utility, either directly or indirectly.

Applicant's references and arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control

mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following:

> "The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Also, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner) and Nagaraja et al. (2006), Waghray et al. (2001) and Sagynaliev et al. (2006) (described below).

Additionally, the majority of the newly cited references by Applicants are drawn to genes known or suspected to be over expressed or under expressed in cancers, and that are involved

with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the protein is important in the development and progression of the cancer. For example, Wang et al. analyzes expression of the cadherins, which are a family of transmembrane proteins that play a crucial role in cell differentiation, cell migration, and intercellular adhesion. Down-regulation of E-cadherin protein had been shown in various human cancers. Wang et al. states: "In conclusion, this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied. This down-regulation may play an important role in the pathogenesis of prostate cancer."

Maruyama et al. studied the expression of Id proteins. Id proteins antagonize basic helix-loop-helix proteins, inhibit differentiation, and enhance cell proliferation. In their study they compared the expression of Id-I, Id-2, and Id-3 in the normal pancreas, in pancreatic cancer, and in chronic pancreatitis (CP), and found increases in both mRNA and protein compared to normal. Maruyama et al. state: "These findings suggest that increased Id expression may be associated with enhanced proliferative potential of pancreatic cancer cells and of proliferating or dysplastic ductal cells in CP."

Manuat et al. teach that vascular endothelial growth factor (VEGF) is the major endothelial mitogen in central nervous system neoplasms and it is expressed in 64-95% of glioblastomas (GBMs). Manuat et al. state "Tumour cells are the main source of VEGF in GBMs whereas VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial ceils. Infiltrating tumour cells and newly-formed capillaries progress through the extracellular matrix by local proteo1ysis involving matrix metalloproteinases (MMPs). Recent studies have shown that VEGF expression and

bioavailability can be modulated by MMPs. We reported previously that the expression of MTI-MMP in human breast cancer cells was associated with an enhanced VEGF expression.....Our results suggest that the interplay between metalloproteinases and VEGF previously described in experimental tumours may also be operative in human GBMs. Because of its dual ability to activate MMP-2 and. to up-regulate VEGF, MTI-MMP might be of central importance in the growth of GBMs and represent an interesting target for anti-cancer treatments."

Rudlowski et al. (cited in IDS filed August 3, 2006), examined GLUT1 mRNA and protein induction in malignant transformation of cervical cancer. The authors state: "We studied whether induction of glucose transporters (GLUTs) 1 to 4 correlates with human papiliomavirus (HPV)-dependent malignant transformation of cervical epithelium. Tissue samples of cervical intraepithelial neoplasia (CIN; grades 1 to 3), invasive carcinomas, and lymph node metastasis were examined. HPV typing was performed. In CIN 3 high-risk HPV lesions, cervical cancer, and metastasis, GLUT1 was expressed at highest levels with a strong correlation of GLUT1 mRNA and protein expression. Immunostains for GLUT2 to GLUT4 were negative. Cervical tumour cells respond to enhanced glucose utilization by up-regulation of GLUTI. The strong induction of GLUTI mRNA and protein in HPV-positive CIN 3 lesions suggests GLUTI over expression as an early event in cervical neoplasia. GLUTI is potentially relevant as a diagnostic tool and glucose metabolism as a therapeutic target in cervical cancer. "

Bea et al. studied gene amplification, mRNA expression and protein expression of the BMI-1 gene, which is a putative oncogene belonging to the Polycomb group family that

cooperates with c-myc in the generation of mouse lymphomas and seems to participate in cell cycle regulation and senescence by acting as a transcriptional repressor of the INK4a/AILF locus. Bea et al. reported that four tumours with gene amplification showed significantly higher mRNA levels and significantly higher protein expression than other MCLs and NHLs with the BMI-1 germ line configuration. Applicants assert that Bea et al. supports the assertion that gene amplification is correlated with both increased mRNA and protein expression. However, as discussed above, it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased protein expression. PRO274 is not a putative oncogene, and the function of the encoded protein is not known.

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification, a single reference, that by Godbout, is pertinent to the issue at hand. However, the Examiner finds applicants interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO274 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumours and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only over expressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the

cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumours, ERBA is not over expressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are over expressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely over expressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons."

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO274 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner cannot find any reason to suspect, that the protein encoded by the PRO274 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumour cell.

In summary, of applicants 118 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO274 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*."

In summary, it is clear that amplification of the genome more often than not does not result in increased mRNA expression.

In conclusion, examination of the papers submitted in the IDS filed August 8, 2006 reveals that the genes/proteins examined were known or suspected to be involved in cancer. Therefore, it is not unexpected that there would be a correlation between mRNA expression and protein expression for proteins that are known or suspected to be involved in development and progression of cancers, or in the case of Bea et al., gene amplification, mRNA expression and protein expression, since expression of the protein may be crucial to that cancers survival, and one mechanism for regulating expression of the protein is the level of mRNA. However, it would not be predictable that an increase in mRNA for a protein of unknown function would also correlate with an increase in the protein. Such is the case in the instant application. The PRO274 is a protein of unknown activity, and has not been shown to be involved in cell proliferation, differentiation and/or cell adhesion/migration.

Other papers submitted with the August 3, 2006 IDS analyzed genes not involved with cancer but with other biological systems/disorders, and found that expression of mRNA and proteins known to be involved with the system or disorder were correlated. For example, Gou and Xie studied the expression and pathogenic role of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome (ARDS), and concluded that the MIF expression level showed a strong correlation with the number of infiltrating macrophages, and that the serum level of MIF and PBMC MIF expression increased in ARDS patients with enhanced pulmonary MIF expression and macrophage infiltration, which suggests that MIF plays a pivotal role in the pathogenesis of ARDS.

Caberlotto et al. had observed specific alteration of neuropeptide Y (NPY) and Y1 receptor mRNA expression in discrete regions of the Flinders Sensitive Line rats (FSL), an animal model of depression, and therefor analyzed mRNA and protein levels. Their results demonstrate a good correlation between NPY peptide and mRNA expression, and the authors concluded that there was possible involvement of NPY-and Y1 receptors in depression.

Again, these papers are drawn to proteins that were known or were suspected to be involved with a specific biological system.

With regard to Applicants' assertions that an increase in transcript levels correlates with an increase in proten levels, Applicants' references and arguments have been considered but not deemed persuasive. With the exception of Futcher et al., all of Applicant's newly cited

references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. Nagaraja et al. (Oncogene, 25:2328-2338, 2006), provide data comparing transcript and protein levels between normal of cancer tissue. Nagaraja et al. characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-

1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO274.

In summary, it is clear that amplification of the genome more often than not does not result in increased mRNA expression and Nagaraja, Waghray and Sagynaliev support the Examiner's position that *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO274. There are no teachings in the specification as to the differential expression of PRO274 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO274 genomic DNA does not support increased mRNA expression, or that even if mRNA levels were increased, the art teaches that there is a poor correlation between mRNA and protein levels. Therefore, the specification and cited

references do not provide a specific and substantial utility for the encoded protein. Further research needs to be done to determine whether the purported increase in PRO274 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and, "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO274 polypeptides and antibodies have utility in the fields of cancer diagnostics is not substantial.

It is believed that all pertinent arguments have been answered.

Conclusion

4. No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER